201-14842A

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

FOR THE DIESTERS CATEGORY OF THE

ALIPHATIC ESTERS CHEMICALS

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

November 14, 2003

EXECUTIVE SUMMARY

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) and its member companies hereby submit the revised test plan for the "diesters" category of "aliphatic esters" chemicals, under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program. The Panel and its member companies used existing available public and company data in conjunction with scientific judgment /analysis to characterize the Screening Information Data Set (SIDS) of human health, environmental fate and effects, and physicochemical property endpoints for the diesters category.

This test plan addresses 13 HPV diesters chemicals listed in Table 1A. The diesters are generally produced from reaction of dicarboxylic acids and monoalcohols. The distinguishing feature of this category of chemicals is that they are diester derivatives of the common diacids: namely, maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acids. The alcohol portion of the diesters generally falls in the C8-C13 carbon number range. In addition, a majority of the HPV diesters in this category fall within the carbon range of C20-C32 and have similar properties and structural characteristics. The diesters in this category have widespread use as lubricants, plasticizers, and solvents.

The chemical and structural similarities of the diesters listed in Table 1A justify grouping these 13 HPV chemicals collectively together under the diesters category of the aliphatic esters. They have close commonalties in their physicochemical properties, chemical characteristics and biological/toxicological activities as a result of the structural diester similarities in their molecules. Grouping these diesters together also represents a rational structural approach: (1) to systematically compare existing data; (2) to justify read-across assessments for structurally related diesters, and (3) to develop a stepwise strategy test plan for the diesters substances based on their ester group type. The diesters as an ester group type are structurally differentiated from other aliphatic ester types such as polyol esters, sorbitan esters, and glycol esters.

In addition to the available data for various HPV diesters in this category, there is published information for four structurally analogous surrogate diesters, which provided useful supplementary data to help bridge the toxicity data gaps for some of the HPV diesters. The four structurally analogous surrogate diesters are: [1] maleic acid, dibutyl ester (CAS 105-76-0); [2] adipic acid, dibutyl ester (CAS 105-99-7); [3] adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3); and [4] adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1).

Measured physicochemical property data were available for many of the HPV diesters. In addition, computer estimation models were used to calculate physicochemical property and environmental fate data for the diesters. The calculated data were obtained using the EPIWIN and EQC (Level III) models that EPA has cited for use in the HPV Chemical Challenge Program. Use of the experimental and calculated values provided the information on the physicochemical and environmental fate properties of the chemicals in the diesters category to satisfy HPV program requirements. No additional testing for physicochemical and environmental fate properties is proposed.

Adequate aquatic toxicity and biodegradation data exist for both the HPV diesters and the structurally analogous surrogate diesters to cover the carbon number range within this category. This allowed for read-across assessments for the HPV diesters. No further aquatic toxicity and biodegradation testing is proposed for diesters category of the aliphatic esters.

The available data on mammalian toxicity (e.g., acute, repeated dose, genetic toxicity, reproductive/developmental toxicity) from both the HPV and surrogate diesters were adequate to cover the SIDS data endpoints for the range of diesters in this category and to permit read-across assessments. Extensive toxicity data were available for maleic acid, dibutyl ester; adipic acid, bis(2-ethylhexyl) ester; adipic acid, tridecyl ester; adipic acid, di-C7-9 branched and linear alkyl esters; and sebacic acid, and bis(2-ethylhexyl) ester. These diesters covered the carbon number range for the HPV diesters in this category and provided useful toxicity data to allow read-across assessments. No additional mammalian toxicity testing is proposed for the diesters category of the aliphatic esters. This resourceful use of the existing data will help to minimize the use of animals for testing while assessing the potential hazards of the substances in the diesters category under the HPV Chemical Challenge Program.

The following member companies of the American Chemistry Council's Aliphatic Esters Panel are sponsoring the Diesters category:

Arizona Chemical Company
BASF Corporation
Cognis Corporation
The CP Hall Company
Crompton Corporation
Cytec Industries Incorporated
ExxonMobil Chemical Company
Inolex Chemical Company
Kaufman Holdings Corporation
Rohm and Haas Company
Sunoco, Incorporated (R&M)
Uniqema
Velsicol Chemical Corporation

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TEST PLAN FOR THE DIESTERS CATEGORY OF THE ALIPHATIC ESTERS

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) and its member companies have committed voluntarily to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and human health effects) for the "diesters" category of aliphatic esters chemicals listed under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program.

This test plan sets forth how the Aliphatic Esters Panel intends to address the testing information for the 13 diesters listed in Table 1A (organized by CAS Numbers in ascending order). The chemicals in this test plan were originally part of a larger test plan submitted on December 20, 2001. As a result of public comments, the Panel has revised the original test plan for these chemicals, and the revised approach follows below.

The chemical structures of the diesters are given in Figure 1. The test plan identifies the CAS Numbers used to characterize the SIDS endpoints for the diesters in this category, describes the chemical and structural features/similarities of the diesters, identifies existing data of adequate quality for substances in the diesters category and provides the Panel's rationale for applying the available SIDS data to characterize the hazards of the category members. The primary objective of this effort is to identify and to characterize the physicochemical properties, mammalian health and environmental fate and effects for the diesters category of the aliphatic esters consistant with the EPA HPV Program.

The data from this HPV category will be used to inform the public about the potential health effects of the diesters category of the aliphatic esters. Developing a data matrix with reliable studies and applying justifiable read-across assessments will help provide a sufficiently robust data set to characterize the endpoints in the HPV Chemical Challenge Program. This approach to the resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the diesters category of the aliphatic esters.

Table 1A: List of Individual Substances in the Diesters Category
(by ascending CAS Numbers and designated TSCA HPV chemical name)

Chemical Name (designated TSCA HPV chemical name)	**CAS Number**
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2
Sebacic acid, dimethyl ester	106-79-6
Adipic acid, bis(1-methylheptyl)ester	108-63-4
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3
Maleic acid, bis(2-ethylhexyl)ester	142-16-5
Adipic acid, diisooctyl ester	1330-86-5
Adipic acid, diisopropyl ester	6938-94-9
Adipic acid, ditridecyl ester	16958-92-2
Adipic acid, diisodecyl ester	27178-16-1

Azelaic acid, diisodecyl ester	28472-97-1
Adipic acid, diisononyl ester	33703-08-1

2.0 DESCRIPTION OF THE DIESTERS CATEGORY

Thirteen CAS Numbers are used to describe the diesters in this HPV category of the aliphatic esters (Table 1A). The "diesters" category of the HPV aliphatic esters is comprised of aliphatic diesters derived from linear diacids and monofunctional alcohols. The diacids include maleic (C4) acid, adipic (C6) acid, azelaic (C9) acid and sebacic (C10) acid. The monofunctional alcohols most common in the diesters are in the C8 to C13 carbon range, although methyl and isopropyl alcohol occur in two of the HPV diesters.

There are two maleic acid, seven adipic acid, two azelaic acid and two sebacic acid diesters on the HPV list for the diesters category. Due to the physicochemical properties of the diesters (e.g., viscosity, pour point), they have widespread applications as lubricants, solvents, and plasticizers (Randles, 1999). The linear diacid portion of the diesters contributes to the good viscosity index while branching in the alcohol portion provides good pour point characteristics. Because diesters have good polarity characteristics, they are useful as solvents. Most of the diesters in this category generally are higher alkyl (>C8) adipates, azelates and sebacates and these diesters generally have a low order of toxicity as will be discussed in Section 4 of this test plan. In addition, diesters derivatives of aliphatic dicarboxylic acids as a general chemical class have been extensively reviewed in Patty's Toxicology (2001) and by the Cosmetic Ingredient Review Expert Panel (Elders, 1984; Andersen, 1996). David et al. (2001) have extensively reviewed and summarized other toxicity endpoints besides the SIDS toxicity endpoints for a number of alkyl maleate, adipate, azelate and sebacate derivatives.

Metabolism of the diesters in animals would be expected to occur initially via enzymatic hydrolysis leading to the corresponding diacids [e.g., maleic, adipic, azelaic and sebacic acids] and the corresponding linear or branched alcohols [e.g., 2-ethylhexyl, 1-methylheptyl, isooctyl, isononyl, isodecyl, tridecyl alcohols]. These diacids and alcohols can be further metabolized or conjugated (e.g., glucuronides, sulfates, etc.) to polar products that are excreted in the urine [Cragg (2001a,b); Bevan (2001b); Thurman (1992)]. The diacids and alcohols are expected to have low orders of toxicity [Cragg (2001a,b); Bevan (2001 a,b); Kennedy (2002); HPV (2001)].

Metabolic hydrolytic reactions of esters have been extensively reviewed in the literature [Testa and Mayer (2003); David et al. (2001); Buchwald (2001); Parkinson (2001); Satoh et al. (1998); Heyman (1982)]. It is beyond the scope of this test plan to discuss or review this topic in more detail except to mention its contribution in the general metabolism scheme for ester linkages.

Organization of 13 HPV Diesters by Parent Diacids/Diesters

Due to the large number of substances in this category, it is useful to organize the 13 HPV diesters on the basis of the parent diacids/diesters (e.g., maleate, adipate, azelate, and sebacate) rather than in the order of their CAS numbers as in Table 1A. Hence, Table 1B organizes the 13 HPV diesters according to the parent diacids and ascending molecular weight within each parent diacid/diester group.

Table 1B. Organization of the 13 HPV Diesters according to Parent Diacids
(e.g., arranged as maleate, adipate, azelate, and sebacate diesters)

Individual Diester (arranged according to parent diacids) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in diacid	Carbon Number in alcohol	Total carbons in diester	MW
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2	C4	C6	C16	284
Maleic acid, bis(2-ethylhexyl)ester	142-16-5	C4	C8	C20	341
Adipic acid, diisopropyl ester	6938-94-9	C6	C3	C12	230
Adipic acid, diisooctyl ester	1330-86-5	C6	C8	C22	370
Adipic acid, bis(1-methylheptyl)ester	108-63-4	C6	C8	C22	370
Adipic acid, diisononyl ester	33703-08-1	C6	C9	C24	399
Adipic acid, diisodecyl ester	27178-16-1	C6	C10	C26	427
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3	C6	C8	C22	435
Adipic acid, ditridecyl ester	16958-92-2	C6	C13	C32	511
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2	C9	C8	C25	413
Azelaic acid, diisodecyl ester	28472-97-1	C9	C10	C29	469
Sebacic acid, dimethyl ester	106-79-6	C10	C1	C12	230
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3	C10	C8	C26	469

The arrangement of the HPV chemicals based on parent diacids/diesters will be useful in comparing and visualizing chemical/structural similarities among the analogous series of diesters in this HPV category and will provide a rational and systematic basis for using existing read-across data to assess structurally analogous or homologous diesters.

As will be described in Section 4, in addition to the existing available data for the 13 HPV diesters in this category, there are significant amounts of relevant published and unpublished toxicity data that also exist for other structurally homologous or analogous diesters (denoted as surrogate diesters) which provide very useful and adequate read-across information.

The four relevant surrogate diesters are:

- Maleic acid, dibutyl ester (CAS 105-76-0)
- Adipic acid, dibutyl ester (CAS 105-99-7)
- Adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) *
- Adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1)

* It should be pointed out that adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) is not on the list of 13 HPV diesters submitted in this test plan. However, Solutia has submitted a separate HPV test plan for hexanedioic acid, di-C7-C9 branched and linear alkyl ester (under 97 Adipate) with the same CAS number. The available toxicity data for this surrogate diester (CAS 68515-75-3) will be used to bridge the toxicity data needs for structurally related adipate diester chemicals in the present HPV diesters test plan.

Incorporation of these four surrogate diesters into Table 1B (based on parent diacids) leads to Table 1C below, which should be useful in the overall HPV data review and test plan evaluation and which should provide reasonable justification (structural, carbon number or MW similarities, etc.) to support read-across assessments.

Table 1C. Organization of the 13 HPV Diesters and 4 Surrogate Diesters according to Parent Diacids for use in HPV Data Assessment and Testing Rationale**

Individual Diester (organized according to parent diacids) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in diacid	Carbon Number in alcohol	Total carbons in diester	MW
** Maleic acid, dibutyl ester	105-76-0	C4	C4	C12	228
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2	C4	C6	C16	284
Maleic acid, bis(2-ethylhexyl)ester	142-16-5	C4	C8	C20	341
Adipic acid, diisopropyl ester	6938-94-9	C6	C3	C12	230
**Adipic acid , dibutyl ester	105-99-7	C6	C4	C14	258
**Adipic acid, di-C7-9 branched and linear alkyl ester	68515-75-3*	C6	C8	C22	356
Adipic acid, diisooctyl ester	1330-86-5	C6	C8	C22	370
Adipic acid, bis(1-methylheptyl)ester	108-63-4	C6	C8	C22	370
** Adipic acid, bis(2-ethylhexyl)ester	103-23-1	C6	C8	C22	370
Adipic acid, diisononyl ester	33703-08-1	C6	C9	C24	399
Adipic acid, diisodecyl ester	27178-16-1	C6	C10	C26	427
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3	C6	C8	C22	435
Adipic acid, ditridecyl ester	16958-92-2	C6	C13	C32	511
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2	C9	C8	C25	413
Azelaic acid, diisodecyl ester	28472-97-1	C9	C10	C29	469
Sebacic acid, dimethyl ester	106-79-6	C10	C1	C12	230
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3	C10	C8	C26	469

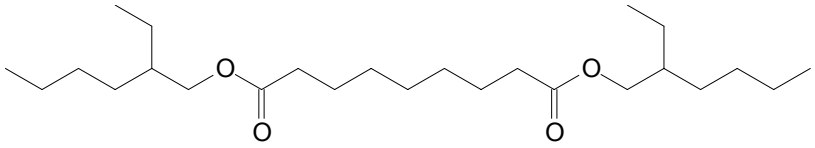
* It should be pointed out that adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) is not on the list of 13 HPV diesters submitted in this test plan. However, Solutia has submitted a separate HPV test plan for hexanedioic acid, di-C7-C9 branched and linear alkyl ester (under 97 Adipate) with the same CAS number. The available toxicity data for this surrogate diester (CAS 68515-75-3) will be used to bridge the toxicity data needs for structurally related adipate diester chemicals in the present HPV diesters test plan.

** These four surrogate diesters (highlighted or shaded) are not part of the present HPV diesters category test plan. They are included in this matrix table since existing toxicity data for these materials can be used for read-across assessment or for bridging data needs to other diesters category members based on their chemical /structural similarities.

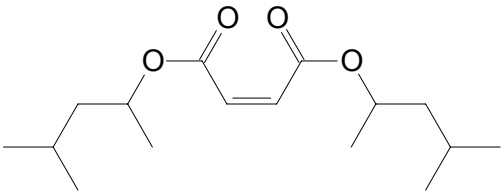
Figure 1. Chemical Structure of the Diesters Listed in Table 1A

The structures of the HPV diesters are given in the order listed in Table 1A, which is organized according to ascending CAS Numbers. The chemical structure depicted for each HPV substance is consistent with the designated CAS Number and is considered representative of the commercial product evaluated.

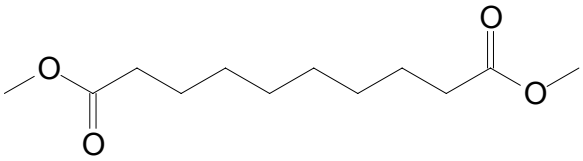
Azelaic acid, bis(2-ethylhexyl)ester (CAS 103-24-2)



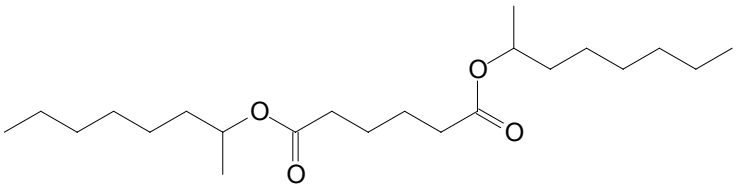
Maleic acid, bis(1,3-dimethylbutyl)ester (CAS 105-52-2)



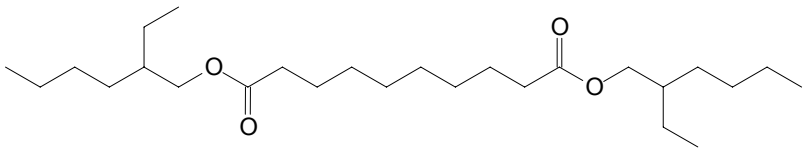
Sebacic acid, dimethyl ester (CAS 106-79-6)



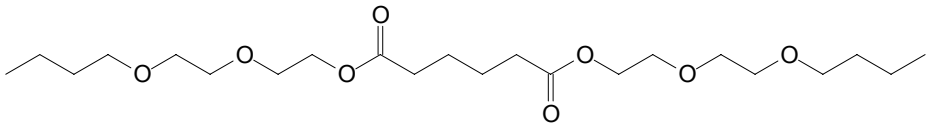
Adipic acid, bis(1-methylheptyl)ester (CAS 108-63-4)



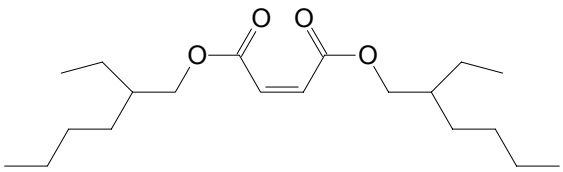
Sebacic acid, bis(2-ethylhexyl)ester (CAS 122-62-3)



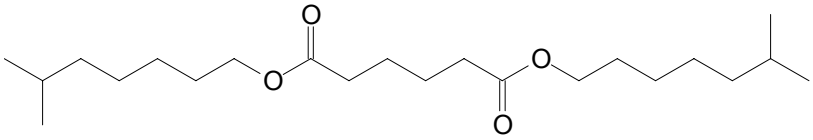
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester (CAS 141-17-3)



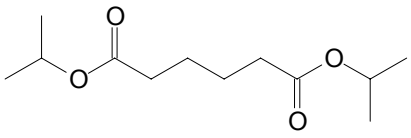
Maleic acid, bis(2-ethylhexyl)ester (CAS 142-16-5)



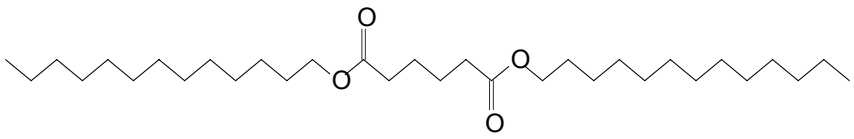
Adipic acid, diisooctyl ester (CAS 1330-86-5)



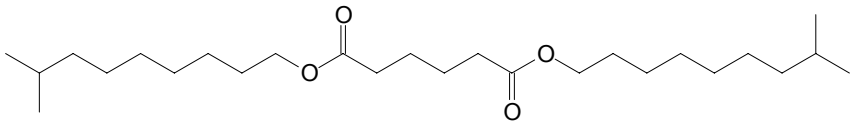
Adipic acid, diisopropyl ester (CAS 6938-94-9)



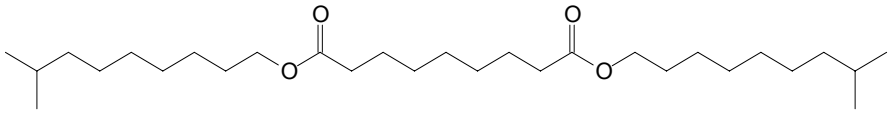
Adipic acid, ditridecyl ester (CAS 16958-92-2)



Adipic acid, diisodecyl ester (CAS 27178-16-1)



Azelaic acid, diisodecyl ester (CAS 28472-97-1)



Adipic acid, diisononyl ester (CAS 33703-08-1)

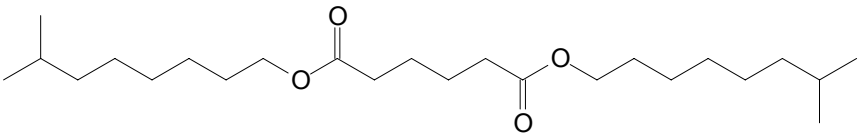
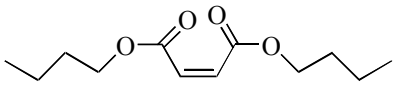
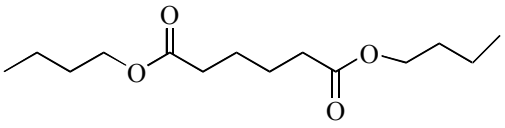


Figure 2. Chemical Structure of Surrogate Diesters

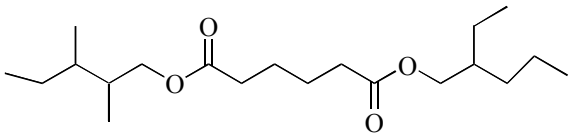
Maleic acid, dibutyl ester (CAS 105-76-0)



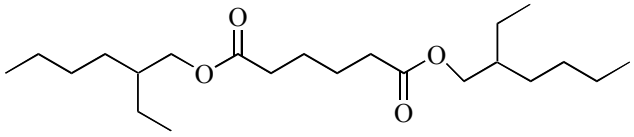
Adipic acid, dibutyl ester (CAS 105-99-7)



Adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3)
(shown is the C7 branched diester structure)



Adipic acid, bis(2-ethylhexyl)ester (CAS 103-23-1)



3.0 DESCRIPTION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and confidential company data was conducted on the physicochemcial properties, mammalian toxicity endpoints, and environmental fate and effects for the 13 diesters using CAS numbers and chemical names. Searches included the following sources: MEDLINE and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook of Chemistry and Physics, IUCLID, Merck Index, and other references) for physicochemical properties.

The reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive reviews [e.g., Patty's Toxicology (2001)]. Safety assessment reviews for some adipates have been reported by Cosmetic Ingredient Review Expert Panel in the Journal of the American College of Toxicology [Elder (1984); Andersen (1996)]. Diesters that were chemically or structurally-related (i.e., homologs, similar carbon number or molecular weight range or bracket) to the HPV diesters were also reviewed to determine whether they were relevant for bridging data needs for environmental fate, aquatic toxicity or mammalian toxicity.

3.1 Physicochemical Properties Data

Physicochemical data [i.e., melting point, boiling point, vapor pressure, water solubility and octanol water partition coefficient (kow)] for the HPV diesters and surrogate diesters were obtained from the searches and sources described above. In addition to available experimental and measured data, calculated physicochemical values were also incorporated into a summary table for all these physical and chemical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements.
- A complete set of physical property data was a prerequisite to calculate fugacity or the chemical distribution in the environment (see below)
- Physicochemical properties data had yet to be developed for some of the diesters.

The physicochemical properties were modeled using the Syracuse Research Corp./EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed for the EPA [EPIWIN (1999); US EPA (1999b)]. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model, a specific discreet structure is required. EPIWIN contains a CAS number database that contains the structures for a large number of chemicals. For mixtures, a single representative structure is contained in the database, and in this test plan these surrogate chemical structures were accepted for further modeling.

3.2 Environmental Fate and Biodegradability Data

Environmental fate data including biodegradability, photodegradation, stability in water (i.e., hydrolysis) and fugacity (chemical distribution in the environment) data were primarily ob-

tained through the literature, from unpublished confidential company data, or from modeling [e.g., EPIWIN, EQC (Level III) - Mackay et al.(1996)]. When relevant studies (particularly biodegradability endpoints) were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch et al. (1997) was utilized to evaluate the data quality of the studies.

3.3 Aquatic Toxicity Data

Existing data for aquatic toxicity studies (e.g., fish, invertebrate and algae) for the HPV and surrogate diesters were obtained primarily from the literature or from unpublished confidential proprietary studies. When relevant studies were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch et al. (1997) was utilized to evaluate the data quality of the aquatic toxicity studies.

3.4 Mammalian Toxicity Data

The existing data for the mammalian toxicity endpoints for the HPV diesters were reviewed using the literature searches to identify the most relevant studies for the substances in the "diesters" category. For some substances, there may have been no relevant studies identified in the searches. For the HPV diesters that contained relevant data, the available studies were reviewed using the criteria outlined in the EPA's methods for determining the data quality and adequacy of the existing data and the reliability ranking method of Klimisch et al. (1997). Relevant studies that were available for the mammalian toxicity endpoints are summarized in the HPV test plan and presented in greater detail in the robust summaries in the Appendix.

Studies that were selected for the robust summaries generally represented the most relevant or reliable data for a particular SIDS endpoint. Published studies from the general literature as well as from a number of unpublished confidential company reports were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of limited experimental details to assess their quality (i.e., not assignable, Klimisch reliability code 4) or only were reported as LD_{50} values from secondary sources. These studies were included in the summary data table and may be included in the robust summaries with reference to the secondary literature source.

4.0 EVALUATION OF EXISTING DATA

The thirteen HPV substances in Table 1A were grouped together under the diesters category of aliphatic esters because they were structurally similar diesters derived from the dicarboxylic acids, maleic, adipic, azelaic and sebacic acids. In addition to the existing data for the 13 HPV diesters, there were read-across data for four surrogate diesters not on the HPV list in this category. Because of their structural similarities, these four surrogate diesters provided useful data for bridging toxicity information for structurally analogous HPV diesters in regard to mammalian toxicity, aquatic toxicity and biodegradability endpoints.

The four surrogate diesters were:

- Maleic acid, dibutyl ester (CAS 105-76-0)
- Adipic acid, dibutyl ester (CAS 105-99-7)
- Adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) *
- Adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1).

The existing data for the HPV diesters and the surrogate diesters have been reviewed. Discussion will be provided in this section regarding the available data for SIDS toxicity endpoints, an assessment and summary of the data, and comments on HPV test plan as to whether the existing data are adequate and whether further testing is needed or planned. The order of discussion of endpoints will be: (1) physicochemical properties; (2) environmental fate and biodegradability; (3) aquatic toxicity; and (4) mammalian health effects.

4.1 Physicochemical Properties Data

Summary of Physicochemical Properties Data

There were significant amounts of reported experimental data for the physicochemical properties (i.e., melting point, boiling point, vapor pressure, water solubility and kow) of the diesters in this category, particularly, for the adipate diesters. In addition, EPIWIN has been used to calculate physicochemical properties for the HPV and surrogate diesters. Experimental physicochemical properties data (measured or those reported in studies, company documents, reference handbooks, secondary literature) and calculated values from EPIWIN for the diesters in this category are summarized in Table 2.

Data Assessment and Test Plan for Physicochemical Properties

In general, the short-chain alkyl (e.g., methyl, isopropyl, and butyl) HPV and surrogate diesters were generally more water soluble, less lipophilic and relatively more volatile than the corresponding longer-chain alkyl (i.e., C8-C13 alcohol) diesters. However, most of the diesters on the HPV list (10 of 13) have molecular weight of greater than 340, have high boiling points (>300°C) and are expected to be relatively non-volatile, lipophilic (log P > 7) and very water-insoluble.

* It should be pointed out that adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) is not on the list of 13 HPV diesters submitted in this test plan. However, Solutia has submitted a separate HPV test plan for hexanedioic acid, di-C7-C9 branched and linear alkyl ester (under 97 Adipate) with the same CAS number. The available toxicity data for this surrogate diester (CAS 68515-75-3) will be used to bridge the toxicity data needs for structurally related adipate diester chemicals in the present HPV diesters test plan.

Based on the summarized experimental and calculated data in Table 2, there are adequate physicochemical data for substances in the "diesters" category and no additional testing will be conducted.

4.2 Environmental Fate and Biodegradability Data

Summary of Environmental Fate and Biodegradability Data

The environmental fate and biodegradability data relevant to the diesters category are summarized in Table 2 and Table 3, respectively. Biodegradability data have been reported for seven of the 13 HPV diesters as well as for the three of the four surrogate diesters (Table 3). These biodegradability tests were mainly performed using OECD test methods with unacclimated inoculum. Most of the diesters tested were demonstrated to be extensively biodegraded.

Other environmental fate endpoints such as photodegradation, stability in water (hydrolysis), and chemical distribution (transport) in the environment (fugacity modeling) have been calculated for the diesters using the EPIWIN and EQC (Level III) models. Calculated hydrolysis half-lives and atmospheric photodegradation rates for the diesters using EPIWIN are summarized in Table 2.

Chemical distribution of the diesters in the environment has been calculated using EQC (Level III), a fugacity-based multimedia model [Mackay et al. (1996)]. The calculated values for the transport (or distribution) in the soil, air, water and sediment environmental compartments are summarized in Table 2. The distribution between the environmental compartments for diesters in this category appears to be influenced by water solubility and lipophilicity. In general, for diesters with higher water solubility characteristics (e.g., diisopropyl adipate and dibutyl adipate, dimethyl sebacate), the EQC model predicted a greater distribution of the test substance in the water compartment. For more lipophilic diesters, the EQC model predicted a greater distribution in soil and sediment.

Data Assessment and Test Plan for Environmental Fate and Biodegradability

As discussed above, seven of the 13 HPV diesters, as well as for the two of the four surrogate diesters, have been adequately tested for biodegradability. More importantly, most of the diesters tested were shown to be readily biodegradable which would indicate that long-chain diesters are capable of undergoing very extensive biodegradation in aerobic aqueous environments, in spite of their low water solubility. Although there are differences in the overall percent biodegradation among the diesters, this is not unexpected given the potential structural differences (e.g., degree of branching in alcohol portion of molecule) and given the water solubility limitations for many of the diesters. Regardless, the existing biodegradability data would suggest that diesters are extensively biodegraded.

In addition, there are data to indicate that lower MW diesters such as dimethyl maleate and dibutyl maleate are readily biodegraded (~95% in 28 days) [IUCLID (1996); OECD SIDS for dibutyl maleate, UNEP (1998)]. Therefore, short-chain alkyl diesters, such as diisopropyl and dibutyl adipates and dimethyl sebacate, would also be expected to biodegrade to a similar extent based on read-across assessment and based on similarities in physicochemical properties such as water solubility, MW, and number of carbons. Since there have been adequate data reported for most of the diesters (e.g., C12 to C32 carbon number range) in this category and

since the majority of the diesters have been shown to be readily biodegradable, no additional biodegradability testing is proposed.

Other environmental fate parameters (i.e., photodegradation, hydrolysis and chemical distribution in environment) have been calculated using the EPIWIN and EQC (Level III) modeling programs. Based on the calculated data for these environmental fate endpoints in Table 2, adequate data exist and that no additional testing is needed.

4.3 Aquatic Toxicity Data

Summary of Aquatic Toxicity Data

Seventeen acute aquatic toxicity studies (e.g., fish, invertebrates and algae) relevant to the diesters category are summarized in Table 3. There are adequate acute toxicity data in fish, daphnids and algae reported for a range of diesters including the maleates, adipates, azelates and sebacates, which collectively cover the carbon number range of C12-C32 for the diesters and which would bracket the range of the 13 HPV diesters in this category. In addition, a recent chronic aquatic toxicity study (*Daphnia magna* reproduction test, OECD 211) has been carried out with the surrogate diester, adipic acid bis(2-ethylhexyl)ester (CAS 103-23-1) at its maximum water solubility limit (measured concentration). The results from this chronic daphnia study should be reflective of similar very water-insoluble and structurally analogous HPV diesters.

Data Assessment and Test Plan for Aquatic Toxicity

Five HPV diesters and three structurally analogous surrogate diesters have been adequately tested for acute toxicity in aquatic organisms (see Table 3 and robust summaries). The acute aquatic studies followed generally accepted test guidelines in which water accommodated fractions (WAFs) were often generated for poorly water-soluble lubricant or petroleum test materials at nominal loading rates and then evaluated for toxicity. However, the ACC Panel believes that in cases where the LC50 or EC50 values (based on nominal loading rates to generate the WAFs) clearly exceed the water solubility of the diester and appears exceeding improbable (e.g., 1000 mg/L or 10,000 mg/L), it would be more appropriate to note that the toxicity endpoint (LC50 or EC50 value) exceeds the maximum water solubility limit (WSL) of the test material. For very water insoluble test materials, the existing data suggest that aquatic toxicity would not be expected at the maximum water solubility limit (WSL) or at water saturated levels, typical of WAF solutions generated from high nominal loading rate concentrations.

In general, the data for a majority of the diesters (except for dibutyl maleate) indicated a low degree of acute toxicity in aquatic species; the actual LL50 or EL50 values were much higher than their calculated maximum water solubility limit (see robust summaries and Tables 2 and 3). Since the long-chain alkyl diesters (e.g., log kow >7 and >C22 total carbon number) have very limited water solubility (Table 2), the available data would indicate that these materials are not likely to cause aquatic toxicity at their maximum water solubility limits (WSL) or concentrations. For example, aquatic toxicity has not been reported in fish, daphnia and algae at saturated water concentrations of bis-2-ethylhexyl adipate (CAS 103-23-1, surrogate diester), which is consistent with its very limited water solubility (Table 2). Similarly, other diesters such as adipic acid, diisononyl ester (CAS 33703-08-1); adipic acid, ditridecyl ester (CAS 16958-92-2); and sebacic acid, bis (2-ethyl hexyl ester (CAS 122-62-3), also showed low de-

grees of aquatic toxicity. These findings are most likely associated with the very low water solubility for the diesters.

Recent findings from a 21-day *Daphnia magna* reproduction study indicate that the surrogate diester, adipic acid, bis(2-ethylhexyl)ester (CAS 103-23-1) did not cause chronic toxicity under static renewal conditions (OECD 211 test guidelines). The no-observed effect concentration (NOEC) based on survival, reproduction and growth over the 21-day exposure was 4.36 µg/L (average) (measured by GC-MS). The exposure concentration was slightly higher but comparable to the reported maximal water solubility limit of adipic acid, bis(2-ethylhexyl) ester, 3.2 to 3.7 µg/L [Letinski et al. (2002); ENSR (2003)]. The results from this chronic daphnia study are likely to be reflective of similar very water-insoluble and structurally analogous HPV diesters.

Overall, there are adequate aquatic toxicity data in fish, daphnids and algae to cover the maleates, adipates, azelates and sebacates in the C12-C32 range for the diesters category. Because of structural similarities between the diesters and because of their very limited water solubility especially for the longer chain alkyl adipates, azelates and sebacates (>C22 total carbon number), the existing aquatic toxicity data (acute and chronic) should be adequate to address the potential aquatic toxicity of the members of the diesters category and, therefore, no additional aquatic toxicity testing will be conducted.

4.4 Mammalian Toxicity Data

A) Acute Mammalian Toxicity

Summary of Available Acute Oral Toxicity Data :

Acute oral toxicity data relevant to the diesters category are summarized in Table 3 and have been reported for 11 of the 13 HPV diesters and four structurally analogous surrogate diesters. There were no deaths when the HPV diesters and the surrogate diesters were administered at doses of >2000 mg/kg. Overall, the acute oral LD_{50} for these substances was greater than the 2000 mg/kg, indicating a very low order of toxicity for the diesters.

Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate acute oral toxicity studies have been conducted for 11 HPV diesters and four structurally analogous surrogate diesters. The data consistently demonstrate a very low order of acute oral toxicity for the diesters in the C12-C32 carbon number range. No additional acute toxicity testing is proposed for substances in the diesters category. It should be mentioned that dermal studies have also been carried out with many diesters that are structurally similar or analogous to the HPV diesters and have been reported to show very low degrees of acute dermal toxicity (see reviews by Elders, 1984; Andersen, 1996; David et al., 2001). The acute dermal toxicity studies of the diesters will not be discussed in any depth here.

B) Mutagenicity and Genotoxicity

Summary of Mutagenicity and Genotoxicity Data

A summary of the mutagenicity and genotoxicity data of HPV substances in the diesters category and structurally analogous surrogate substances are presented in Table 3. Either bacterial or mammalian gene mutation assays, *in vitro* chromosomal aberration assays, or *in vivo* chromosomal

aberration assays have been conducted for these substances. Neither mutagenicity nor clastogenicity were exhibited by any of these diesters in the cited *in vivo* or *in vitro* tests, with or without metabolic activation.

Bacterial Gene Mutation Assay

Three HPV diesters [i.e., CAS 16958-92-2; CAS 33703-08-1; CAS 122-62-3] have been adequately tested in bacterial reverse mutation tests. All tested substances were negative for mutagenicity activity, with and without metabolic activation. The two surrogate adipate diesters [adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1; surrogate) and adipic acid, di-C7-9 branched and linear alkyl esters (CAS 68515-75-3; surrogate)] have also been evaluated for mutagenicity and were found to be negative in bacterial reverse mutation assay. Although the two HPV maleate diesters have not been tested, it has been reported that dibutyl maleate (CAS 105-76-0; surrogate) is negative in the bacterial reverse mutation assay (Table 3). All tested substances were negative for mutagenic activity, with and without metabolic activation.

Mammalian Cell Gene Mutation Assay

Diisononyl adipate (CAS 33703-08-1) was negative in the mouse lymphoma assay, with and without metabolic activation. In addition, adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1; surrogate diester) has been evaluated for mutagenicity and was found to be negative in the mouse lymphoma assay, with and without metabolic activation.

In vitro Chromosomal Aberration Assay

The surrogate substance, adipic acid bis(2-ethylhexyl) ester (CAS 103-23-1) did not cause chromosomal aberrations in the Chinese hamster ovary cell assay or the mouse micronucleus test, with and without metabolic activation of the test material.

In vivo Chromosomal Aberration Assay

The HPV substance, adipic acid, ditridecyl ester (CAS 16958-92-2) was negative in the micronucleus test in the mouse (*in vivo)*. The two surrogate diesters, dibutyl maleate (CAS 105-76-0) and adipic acid bis(2-ethylhexyl) ester (CAS 103-23-1), have been adequately tested in *in vivo* chromosomal aberration assays. Both were negative in the mouse micronucleus test *in vivo*.

Data Assessment and Test Plan for Mutagenicity and Genotoxicity

Three HPV and three surrogate diesters have been adequately tested for gene mutations in bacterial cells, with and without metabolic activation. Although only one HPV diester has been tested for genotoxicity, two surrogate diesters (structural analogs which cover C12 to C22 carbon number range) have been tested for bracketing the genotoxicity of the diesters category. The data consistently demonstrated no evidence of mutagenicity or genotoxicity regardless of metabolic activation of diesters covering the carbon number range of C12-C32. This suggests that members of the diesters category and related structural analogs lack genotoxicity due to their functional similarity in chemical structures and supports reasonable justification for bridging data gaps within this HPV Challenge Program.

By bridging these data, members of the diesters category have been evaluated adequately for genotoxicity, and no additional testing is proposed under the HPV Program.

C) Repeated-Dose Toxicity

Summary of Repeated-Dose Toxicity Data

The HPV Challenge Program requires that a repeated-dose toxicity study and a reproductive toxicity study (see below) be performed or bridged to structurally analogous substances. Adequate data on repeated dose toxicity are available for diisononyl adipate (CAS 33703-08-1), ditridecyl adipate (CAS 16958-92-2), and sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3). In addition, adequate data for repeated-dose toxicity are available for three structural analogous surrogate diesters.

Repeated-Dose Oral Toxicity

In 90-day toxicity studies, rats were administered diisononyl adipate (CAS 33703-08-1) in the diet at levels equivalent to 0, 50, 150 and 500 mg/kg/day. The NOAEL was 500 mg/kg/day. Feeding studies were also carried out in beagle dogs for 13 weeks at dietary concentrations of 0, 0.3, 1 and 3% (increased to 6% at week 9). The NOAEL was determined to be 1% in the diet or approximately 274 mg/kg/day. When sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3) was evaluated in a 3-week feeding study and a 19-month feeding study in rats, the LOAEL was ~1000 mg/kg/day (2% diet) and the NOAEL was 200 ppm diet, respectively.

In addition, 90-day subchronic dietary studies have been adequately carried out with two surrogate adipates: namely, adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) and adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1). For CAS 68515-75-3, rats were fed 0, 0.1, 0.5 and 2.5% of the test substance in the diet. No significant signs of toxicity were observed in male and female rats administered the test material in the diet at concentrations up to 2.5% for a period of 13 weeks. The NOAEL was 2.5% for both sexes (males ~1500 mg/kg; females ~1950 mg/kg). In the 90-day dietary studies with 2-ethylhexyl adipate (CAS 103-23-1; surrogate diester), the NOAEL was ~300 mg/kg/day in rats and ~230 mg/kg/day in mice. The LOAEL was ~600 mg/kg/day in rats and ~460 mg/kg/day in mice. Hepatic hypertrophy and increased peroxisomal enzyme activity occurred in rats and mice; however, there were no adverse effects on the liver. In addition, repeated dose studies have been reported also for the surrogate diester, dibutyl maleate (CAS 105-76-0; see Table 3). The NOAEL was reported to be 95 mg/kg/day.

Results from these studies showed a low order of repeated-dose toxicity and are summarized in Table 3.

Repeated-Dose Dermal Toxicity

In a 13-week study, ditridecyl adipate (CAS 16958-92-2) was applied to the skin of rats, five days a week for thirteen weeks at dose levels of 800 and 2000 mg/kg/day. Based on test results, ditridecyl adipate was well tolerated in rats given dermal doses of 800 and 2000 mg/kg/day.

Data Assessment and Test Plan for Repeated-Dose Toxicity

Sufficient repeated-dose toxicity studies using different animal species (e.g., rats, mice, dogs) and oral and dermal routes of administration have been conducted with diesters in the C12-C32 carbon number range. These data suggest that members of the diesters category and structurally related surrogate diesters exhibit a low order of toxicity following repeated applications, and due to their

chemical and structural similarities, the existing data support reasonable justification for bridging data needs within this HPV Challenge Program.

By bridging these data, members of the diesters category have been evaluated adequately for repeated exposure toxicity, and no additional testing will be conducted.

D) Reproductive/Developmental Toxicity

Summary of Reproductive/Developmental Toxicity Data

A reproductive/developmental study of sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3) has been reported in the scientific literature. No other reproductive toxicity studies have been conducted for members of the "diesters" category; however, data are available for two surrogate diesters (CAS 105-76-0 and 103-23-1). The HPV diester, adipic acid, ditridecyl ester (CAS 16958-92-2), has been tested for developmental toxicity. Three structural analogous surrogate diesters have been tested for developmental toxicity. Results from these studies showed a low order of reproductive/developmental toxicity and are summarized in Table 3.

Reproductive Toxicity

In a 13-week dermal study with ditridecyl adipate (CAS 16958-92-2), there were no sperm morphological changes observed in male rats treated at levels of 2000 mg/kg. Increases in organ weight of the epididymides and uterus were observed following dermal exposure at 2000 mg/kg but not at 800 mg/kg. The scientific literature reports that no adverse reproductive, suckling and growth affects were evident in a four-generation study in rats fed a diet containing 200 ppm sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3) (BIBRA, 1996). The surrogate diester, di-2-ethylhexyl adipate (CAS 103-23-1) has been evaluated for reproductive effects in a one-generation study. Male and female rats were administered di-2-ethylhexyl adipate in their diets at dose levels of 0, 28, 170 or 1080 mg/kg/day. After 10 weeks on the diet, the animals were mated to produce one generation of offspring. Test diets were fed continuously throughout the study (18-19 weeks of exposure). No effects were seen on male or female fertility. However, at the highest dose, there was a reduction in body weight in the dams, and reduction in offspring body weight, total litter weight and litter size. The NOAEL and LOAEL for this study was 170 and 1080 mg/kg/day, respectively (ICI, 1988a). The surrogate diester, dibutyl maleate (CAS 105-76-0) has been evaluated in an OECD reproductive/developmental toxicity screening test (oral gavage) and no adverse effects on reproduction were reported [OECD SIDS dossier for dibutyl maleate, UNEP (1998)].

Developmental Toxicity/Teratology

Two developmental studies have been carried out with adipic acid, ditridecyl ester (CAS 16958-92-2) following dermal application in rats. One study reported an increased incidence of levocardia at a dose of 2000 mg/kg. The NOAEL in this study was 800 mg/kg for developmental effects with maternal toxicity. In a subsequent study with larger number of pregnant dams, offsprings did not show levocardia or other developmental toxicity at a dose of 2000 mg/kg (dermal application). No evidence of developmental toxicity was observed at dose levels of 1000 and 4000 mg/kg/day after oral gavage of the surrogate diester, adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3). Slight maternal toxicity (reduced body weight) and embryotoxicity (reduced fetal weight) was observed at the highest dose (7000 mg/kg/day). The NOAEL for maternal and developmental toxicity was 4000 mg/kg/day. As discussed previously, no adverse developmental, suckling and growth affects were evident in a

four-generation study in rats fed a diet containing 200 ppm sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3, surrogate diester) (BIBRA, 1996; Lefaux; 1968). In addition, no adverse developmental effects were reported for the surrogate diester, dibutyl maleate (CAS 105-76-0; surrogate) in an OECD reproductive/developmental screening study**.**

The developmental toxicity has also been evaluated for the structural analog, adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1; surrogate diester) by dietary exposure. Pregnant rats administered 2-ethylhexyl adipate in the diet throughout gestation showed reduced body weight at dietary equivalent doses of 1080 mg/kg/day. At 1080 mg/kg/day, implantation fetal loss was evident; however, no gross, skeletal or visceral abnormalities were observed. LOAEL was 1080 mg/kg/day and NOAEL was 170 mg/kg/day for developmental toxicity (ICI, 1988b).

Data Assessment and Test Plan for Reproductive/Developmental Toxicity

Since these five materials cover the carbon number range of C12-C32 for the diesters and because of the structural similarity of these alkyl diesters, the available reproductive/developmental toxicity data support reasonable justification for bridging data needs within this HPV category. These data are considered adequate to address the potential reproductive/developmental toxicity of members of the diesters category and no additional reproductive/developmental toxicity tests are proposed.

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that adequate health effects and toxicity data exist for the diesters category of the aliphatic esters (taking into account data available for structurally related and analogous surrogate diesters) to substantially characterize the mammalian health effects, aquatic toxicity and biodegradation endpoints for all the members of this category under the HPV program (Table 4). No additional toxicity tests are proposed for the diesters category of the aliphatic esters. Thus, the resourceful use of the existing data will help to minimize the use of animals for testing and at the same time assess the potential hazards of the substances in the diesters category to satisfy the HPV Chemical Challenge Program.

Table 4. Assessment Plan for Substances in the Diesters Category under the HPV Program

Diester	Total Carbon No. MW	Mammalian Health Effects						Ecotoxicity - Biodegradability			
		Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
* Maleic acid, dibutyl ester	C12 228	√	√	√	√	√	R	√	√	√	√
Maleic acid, bis(1,3-dimethylbutyl)ester	C16 284	√	R	R	R	R	R	R	R	R	R
Maleic acid, bis(2-ethylhexyl)ester	C20 341	√	R	R	R	R	R	R	R	R	R
Adipic acid, diisopropyl ester	C12 230	√	R	R	R	R	R	R	R	R	R
* Adipic acid, dibutyl ester	C14 258	√	--	--	--	--	--	--	--	--	--
* Adipic acid, di-C7-9 branch and linear alkyl esters	C22 356	√	√	√	--	--	√	√	√	√	√
Adipic acid, diisooctyl ester	C22 370	√	R	R	R	R	R	R	R	R	√
Adipic acid, bis(1-methylheptyl)ester	C22 370	√	R	R	R	R	R	R	R	R	R
* Adipic acid, bis(2-ethylhexyl)ester	C22 370	√	√	√	√	√	√	√	√	√	√
Adipic acid, diisononyl ester	C24 399	√	√	√	R	R	R	√	R	R	√
Adipic acid, diisodecyl ester	C26 427	√	R	R	R	R	R	R	R	R	√
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	C22 435	R	R	R	R	R	R	R	R	R	R
Adipic acid, ditridecyl ester	C32 511	√	√	√	√	R	√	√	√	R	√
Azelaic acid, bis(2-ethylhexyl)ester	C25 413	√	R	R	R	R	R	√	R	R	√
Azelaic acid, diisodecyl ester	C29 469	√	R	R	R	R	R	√	R	R	√
Sebacic acid, dimethyl ester	C12 230	R	R	R	R	R	R	R	R	R	R
Sebacic acid, bis(2-ethylhexyl)ester	C26 469	√	√	√	R	√	R	√	√	√	√

* Shaded (highlighted) areas denote surrogate diester substances - their data are included in table to help bridge data needs for structurally analogous HPV diesters, -- denotes that no data for specific toxicity endpoint heading available for this surrogate diester.

Abbreviations in table:
√ = adequate existing data available,
R = read-across data from structurally analogous diesters

Adequate experimental and calculated data for physicochemical properties (i.e., melting point, boiling point, vapor pressure, water solubility and octanol-water partition coefficient) exist for the diesters in this category. No further testing is proposed for these endpoints for the diesters category of the aliphatic esters.

In addition, there are adequate experimental or calculated data for environmental fate endpoints such as biodegradability (see below), photodegradation, hydrolysis and chemical distribution in the environment (via fugacity modeling) for the diesters in this category. No further testing is proposed for these endpoints for the diesters category.

Adequate aquatic toxicity and biodegradation data exist for both the HPV diesters and the structurally analogous surrogate diesters to cover the carbon number range within this category. This allowed for read-across assessments and for bridging data gaps for the HPV diesters. No further aquatic toxicity and biodegradation testing is proposed for diesters category of the aliphatic esters.

Robust summaries of existing health effects, environmental fate and effects, and physicochemical properties data are attached in the Appendix. Summaries of other environmental fate endpoints are also included. Existing data for the structurally analogous surrogate diesters are either included in robust summaries or are referenced in the Appendix should they have been reviewed or summarized elsewhere (such as existing SIDS, HPV test plans) in the literature/public domain. This test plan is expected to provide adequate information to substantially characterize the mammalian health effects, physicochemical properties and environmental fate and effects (including aquatic toxicity, biodegradability) endpoints for the diesters category of the aliphatic esters under the HPV Chemical Challenge Program.

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* The list of references is not a comprehensive bibliography of the literature for the HPV diesters substances. Pertinent papers cited in the text are those that are important in health hazard assessments or in bridging toxicity data for structurally analogous surrogate diesters (e.g., maleate, adipates, sebacates). The information and data in the papers and reviews supplement the robust summaries developed for the toxicology studies of the HPV substances, which are ultimately used to address the SIDS toxicity endpoints for the diesters in this HPV test plan.

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7.0 List of Tables and Figures

Table 2. Summary Table of Physicochemical Properties and Environmental Fate Data for the Diesters

Diesters Category of Aliphatic Esters include the Maleates, Adipates, Azelates, Sebacates

Total Carbon Number in Diester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (mm Hg @ 25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Chemical Distribution (Transport) within Environmental Compartments- Fugacity Model			
											Soil %	Air %	Water %	Sediment %
12	228	105-76-0	Maleic acid, dibutylester	< -60 -28 c	277-280 267 c	<1 E-02 hPa (20 C) 5.32 E-03 c	3.38 4.16 c	173 (20 C) 8.7 c	0.33 c	0.33 c	55.9 c	2.7 c	39.3 c	2.2 c
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	-28 c	292 c	0.0297 c	5.8 c	0.16 c	0.23 c	12.2 c	37.3 c	0.9 c	16.4 c	45.3 c
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	-60 29 c	164 (10mmHg) 360 c	7.2 E-05 c	7.9 c	0.00117 c	0.19 c	0.52 c	29.6 c	1.1 c	11.2 c	58.1 c
12	230	6938-94-9	Adipic acid, diisopropyl ester	-1 -48 c	120 (6.5 mmHg) 241 c	0.0446 c	3.2 c	55.6 c	1.03 c	2.33 c	58.8 c	2.7 c	38.0 c	0.6 c
14	258	105-99-7	Adipic acid, dibutyl ester	-32 -6.6 c	165 (10 mm Hg) 294 c	0.00273 c	4.33 c	4.2 c	0.84 c	2.07 c	54.0 c	3.6 c	39.3 c	3.1 c
22	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters	30 c	224 361 c	13 hPa @ 224C 8.89 E-03 c	> 6.48 7.55 c	<0.048 0.0020 c	0% (14 days) 0.45 c	3.21 c	27.3 c	0.3 c	3.6 c	68.8 c
22	370	1330-86-5	Adipic acid, diisooctyl ester	-70 9 c	205-220 (4 mmHg) 379 c	<0.12 (150 C) 3.53 E-03 c	8.12 c	5.45 E-04 c	0.45 c	2.07 c	27.3 c	0.3 c	3.5 c	69.0 c
22	370	108-63-4	Adipic acid, bis(1-methylheptyl) ester	9 c	175 (2 mmHg) 379 c	2.65 E-05 c	8.1 c	0.00545 c	0.42 c	2.33 c	29.5 c	1.2 c	11.1 c	58.2 c
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl) ester	-67.8 9 c	417 214 (5 mm Hg) 379 c	0.021 hPa (100 C) 3.5 E-05 c	8.12 c	3.2 E-03 (1) 5.45 E-04 c	0.40 c	3.2 c	31.4 c	1.0 c	10.8 c	56.8 c
24	399	33703-08-1	Adipic acid, diisononyl ester	-60 56 c	233 (5 mm Hg) 416 c	0.9 (200 C) 2.25 E-04 c	9.24 c	2.2 E-04 (1) 3.98 E-05 c	0.40 c	4.64 c	28.8 c	0.6 c	7.2 c	63.4 c
26	427	27178-16-1	Adipic acid, diisodecyl ester	-71 51 c	239-246 (4mm Hg) 426 c	1.3 E-03 (20 C) 1.51 E-04 c	10.1 c	4.4 E-05 (1) 5.15 E-06 c	0.36 c	2.07 c	28.5 c	0.2 c	3.4 c	67.9 c
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	117 c	441 c	9.84 E-08 c	3.2 c	3.2 c	0.15 c	0.81 c	71.7 c	0.0 c	27.8 c	0.4 c
32	511	16958-92-2	Adipic acid, ditridecyl ester	141 c	509 c	1.45 E-07 c	13.17 c	3.43 E-09 c	0.28 c	4.64 c	31.0 c	0.4 c	7.0 c	61.7 c
25	413	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	-78 41 c	237 (5 mmHg) 414 c	5 (237 C) 1.66 E-05 c	9.6 c	1.65 E-05 c	0.36 c	3.22 c	28.4 c	0.6 c	7.2 c	63.8 c
29	469	28472-97-1	Azelaic acid, diisodecyl ester	83 c	460 c	7.61 E-08 c	11.6 c	1.54 E-07 c	0.32 c	2.1 c	29.8 c	0.2 c	3.4 c	66.6 c
12	230	106-79-6	Sebacic acid, dimethyl ester	38 -27 c	175 (20 mm Hg) 261 c	0.011 c	3.4 c	120 41.7 c	1.1 c	3.6 c	60.1 c	2.5 c	36.7 c	0.7 c
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl)ester	-48 51 c	212 (1mm Hg) 256 (5mm Hg) 426 c	1.97 E-06 c	3.74 10.1 c	1.5 E-07 c	0.35 c	7.1 c	28.7 c	0.5 c	7.2 c	63.6 c

Highlighted rows denote surrogate diesters not on the HPV diesters category list but which were included in Table to facilitate read-across assessments or to bridge data needs owing to their chemical/structural similarities.

c = calculated data using EPIWIN or EQC (Level III); all other values in table are derived from measurements or data obtained from company reports, documents, MSDS, reference handbooks, secondary literature sources.

* Mixtures are expected to have melting points below those of pure components. Modeled data may not accurately reflect melting points for these substances.

** Many of the diesters substances have boiling points determined under reduced pressure (mm Hg reduced pressure given in parenthesis).

(1) Recent water solubility data were determined by the slow-stir method of D. Letinski et al Chemosphere 48: 257-265 (2002).

Table 3. Summary Table of Mammalian Health Effects, Ecotoxicity and Biodegradation Data for the Diesters

				Mammalian Health Effects						Ecotoxicity and Biodegradation			
Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Reproductive Toxicity	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia EC50 or EL50	Algal EC50 or EL50	Biodegradation %
12	228	105-76-0	Maleic acid, dibutyl ester (a)	3.73 g/kg	Combined repeated dose/reprod screening study at 20, 95 and 300 mg/kg/day (oral gavage) in male and female rats NOAEL 95 mg/kg/day.	Negative (Ames)	Negative (micronucleus, in vivo, mouse)	No adverse effect reported on reproductive performance in repeated dose/ reprod screening study. NOAEL 95 mg/kg/day	No adverse developmental effects were reported in reproductive screening study	1.2 mg/L	21 mg/L	6.2 mg/L	Readily Biodeg. 95% in 19 days OECD 301E
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	7.46 g/kg									
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	> 10 ml/kg									
12	230	6938-94-9	Adipic acid, diisopropyl ester	> 3.11 g/kg (b)									
14	258	105-99-7	Adipic Acid, dibutyl ester	12.9 g/kg									
22	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters (c)	>13.8 g/kg	90-Day Oral Diet (rat) NOAEL 2.5% diet ~1500 mg/kg/d male NOAEL 2.5% diet ~1950 mg/kg/d female	Negative (Ames)		NOAEL 4000 mg/kg maternal tox in develop study (rats, oral) 90-Day oral diet study - no adverse effects to reprod organs	Develop / teratology study rats (oral gavage) NOAEL 4000 mg/kg embryo/fetotoxicity NOAEL 7000 mg/kg teratogenicity	> 1000 mg/L Aq. toxicity not expected at WSL*	1.9 mg/L	1.8-2.5 mg/L	67-88% OECD 302A + CO2 evolut methods
22	370	1330-86-5	Adipic acid, diisooctyl ester	> 5 ml/kg (d)									Readily Biodeg. 86.76% in 28 days OECD 301B
22	370	108-63-4	Adipic acid, bis(1-methylheptyl)ester	> 64 g/kg									
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl)ester (e)	7.392 g/kg 9.1 g/kg	90-Day Oral (diet) LOAEL (rat) ~600 mg/kg/day; (mouse) ~460 mg/kg/day NOAEL (rat) ~300 mg/kg/day, (mouse) ~230 mg/kg/day	Negative (Ames; CHO in vitro, mouse lymphoma)	Negative (micronucleus, in vivo)	One-generation reprod. oral diet (rat) LOAEL = 1080 mg/kg/d NOAEL = 170 mg/kg/d No effect on male or female fertility.	Develop study - oral diet (rat) LOAEL = 1080 mg/kg/d NOAEL = 170 mg/kg/d	54-130 mg/L Aq. toxicity not expected at WSL*	Acute > 500 mg/L Aq. toxicity not expected at WSL* 21-day daphnia reprod showed no chronic tox at saturated water conc (measured)	> 500 mg/L Aq. toxicity not expected at WSL*	Readily Biodeg 67-74% in 28 days OECD 301C (MITI), 94% in 35 days OECD 301B (CO2)
24	399	33703-08-1	Adipic acid, diisononyl ester	> 10 g/kg	90-Day Oral Diet NOAEL 500 mg/kg/day (rat) NOAEL 274 mg/kg/day (dog)	Negative (Ames, mouse lymphoma)				> 2.6 mg/L Aq. toxicity not expected at WSL*			Readily Biodeg. 73% in 28 days OECD 301F
26	427	27178-16-1	Adipic acid, diisodecyl ester	20.5 g/kg									Readily Biodeg. 76.46% in 28 days OECD 301F
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester										
32	511	16958-92-2	Adipic acid, ditridecyl ester	>15 g/kg; >16 g/kg	90-Day Dermal (rat) Doses of 800 and 2000 mg/kg/d were well tolerated.	Negative (Ames)	Negative (micronucleus in vivo)	90-day Dermal Study (rat) at 800 and 2000 mg/kg/d showed no effect in reprod. tissues, sperm morphology or epididymides and uterus wt	Two dermal develop tox studies (rats). NOAEL 800 mg/kg develop tox with maternal tox in one study. No develop effects in second study at 2000 mg/kg	>5000 mg/L Aq. toxicity not expected at WSL*	4800 mg/L Aq. toxicity not expected at WSL*		Not Readily Biodeg 57-60% in 28 days OECD 301B
25	413	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	8.72 ml/kg						>10,000 mg/L Aq. toxicity not expected at WSL*			Readily Biodeg. 81% in 28 days OECD 301B
29	469	28472-97-1	Azelaic acid, diisodecyl ester	>2 g/kg						>10,000 mg/L Aq. toxicity not expected at WSL*			Primary Biodegrad. Results Only
12	230	106-79-6	Sebacic acid, dimethyl ester										
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl) ester (f)	>12.8 g/kg (rats) 9.5 g/kg (mice) 17 g/kg (rats)	3-Week 2% Diet, oral (rat) - LOAEL 1000 mg/kg/day, Liver weight increase and peroxisome proliferation reported. 19-Month Oral diet (rat) - NOAEL 200 ppm (see reprod/develop)	Negative (Ames)		19 mo. (four-generation) dietary feeding study at 200 ppm (~10 mg/kg/d). No reprod/develop toxicity. No histological evidence of abnormality reported in reproductive tissues.	No developmental toxicity was reported in 19 mo. four-generation dietary feeding study. Reprod., suckling and growth were normal.	>1000 mg/L Aq. toxicity not expected at WSL*	>1000 mg/L Aq. toxicity not expected at WSL*	>1000 mg/L Aq. toxicity not expected at WSL*	Not Readily Biodeg. 65% in 28 days OECD 301B

Highlighted rows denote surrogate diesters not on the HPV diesters category list but which were included in the table to facilitate read-across assessments or to bridge data needs owing to their chemical/structural similarities.

(a) Toxicity data for dibutyl maleate were reported in OECD SIDS dossier for Maleic acid, dibutyl ester (CAS 105-76-0)(UNEP, 1998). Toxicity data for dibutyl maleate have also been reported and reviewed in IUCLID (1996).

(b) LD50 value reported by RL Elder, Final safety assessment of dioctyl adipate and diisopropyl adipate. J. Am. Coll. Toxicol. 3(3): 101-130 (1984). Robust summary has limited experimental information from secondary literature source.

(c) It should be noted that adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) was not on the list of 13 HPV diesters in this test plan. However, Solutia has submitted a separate HPV test plan for hexanedioic acid, di-C7-C9 branched and linear alkyl ester (under 97 Adipate) under this CAS No. The available toxicity data for this surrogate diester (CAS 68515-75-3) will be used to bridge the toxicity data needs in the present HPV diesters test plan.

(d) LD50 value and toxicity findings have been reported in secondary literature reference (R. Lefaux, Practical Toxicology of Plastics, 1968). Robust summary has limited experimental information that is mainly cited from secondary reference.

(e) Toxicity data for di(2-ethylhexyl) adipate (CAS 103-23-1) have been reviewed and summarized in Patty's Toxicology [David et al. (2001)], in BIBRA Toxicity Profile (1991), IUCLID (2000).

(f) Toxicity data for di(2-ethylhexyl) sebacate (CAS 122-62-3) have been reviewed and summarized in a BIBRA Toxicity Profile document (1996)

* WSL = Water solubility limit or water saturation level. Aquatic toxicity not expected at maximum WSL (either calculated or measured) of test material based on findings at nominal loading rate or water accommodated fractions (WAF).